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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,522	11/21/2001	Choy-Pik Chiu	097/002	3556

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,522	CHIU ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/23/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants elected without traverse in the amendment filed on 4/7/03 the following species: (a) the first cell population has characteristics of mesenchymal stem cells; (b) the first cell population expresses CD90; and (c) the second cell population comprises cardiomyocytes or their lineage-restricted precursors.

Claims 1-20 are pending in the present application, and they are examined on the merits herein with the aforementioned elected species.

Priority

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) **in the first sentence of the specification** of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number. At the moment, **the priority reference is still in the second paragraph of the first page of the specification.**

Claim Objections

Claims 4-7, 11-13, 15 and 17 are objected to because the claims contain non-elected species. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to **make and/or** use the invention for the same reasons already set forth in the previous Office Action mailed on 6/18/03 (pages 3-8).

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

With respect to the elected invention, the instant claims are drawn to a combination of pharmaceutical compounds comprising: (a) a first cell population that has been differentiated from human pluripotent stem (hPS) cells into a phenotype that renders a subject to whom it is administered immunotolerant to a second cell population that is differentiated from hPS cells and is MHC compatible with the first cell population, wherein the first cell population has characteristics of mesenchymal stem cells or one

that expresses CD90 cell marker and the second cell population comprises cardiomyocytes; a method for preparing the same cell populations for therapeutic use as well as methods for reconstituting cellular function or preparing an individual for therapy to reconstitute their cellular function using the same.

The instant specification describes in general that human ES cells can be differentiated into tolerizing cells by forming embryoid bodies or by direct differentiation in a suitable culture environment with suitable medium, and that relevant markers for mesenchymal stem cells are: CTLA-4, SH2+, SH3+, CD29+, CD44+, CD71+, CD90+, CD106+, CD14-, CD34-, CD45-. Additionally, the present disclosure states that scientists at Geron Corporation have discovered that it is possible to differentiate hPS cells into a highly enriched population comprising cardiomyocytes or cardiomyocyte precursors.

However, the instant specification is not enabled for the presently claimed invention for the following reasons.

(1) The breadth of the claims. The instant claims encompass a combination of pharmaceutical compounds comprising: (a) a first cell population that has been differentiated from human pluripotent stem (hPS) cells into a phenotype that renders any subject to whom it is administered immunotolerant to a second cell population that is differentiated from hPS cells, not necessarily derived from the same hPS cells, and is MHC compatible with the first cell population, wherein the first cell population has characteristics of mesenchymal stem cells or one that expresses CD90 cell marker and the second cell population comprises cardiomyocytes; a method for preparing the same

cell populations for therapeutic use as well as methods for reconstituting cardiomyocyte function or preparing an individual for therapy to reconstitute cardiomyocyte function using the same by administering the first and second cell populationd by any route of delivery into the individual.

(2) The state and unpredictability of the prior art. At the effective filing date of the present application, little is known about tolerance induction and/or cardiac repair or regeneration for human allograft patients using cell populations differentiated from human pluripotent stem cells (Waldmann, Nature Med. 5:1245-1248, 1999; IDS; Sussman, Nature 410:640-641, 2001). Kaufman et al. (PNAS 98:10716-10721, 2001) state "**If** human ES cell-derived HSCs can be used to create hematopoietic chimerism in a patient, that patient should be tolerant to other tissues derived from the same ES cells and would not require any continuous immunosuppressive treatment", and "The clinical promise of human ES cell-base therapies is great; however, because these therapies will be entirely novel, serious concerns about safety and efficacy will need to be addressed before human clinical trials can be initiated" (page 10721, col. 1). Furthermore, in a post-filing art (Nature Med. 8:171-177, 2002; IDS), Fandrich et al. also note that the potential for mouse or human embryonic stem cells or their progenitor cells to survive in an allogenic host environment has not been reported, even in 2002 (page 176, col. 2, second full paragraph).

With respect to the utilization of cardiomyocytes in cardiac muscle repair and/or regeneration, Grounds et al. (J. Histochem. Cytochem. 50:589-610, 2002) state "Although some experiments in animal models report successful engraftment and

maturation of embryonic cardiomyocytes in normal and injured hearts ...., other studies show that most of the donor cardiomyocytes (engrafted into mature rat hearts after infarction) retained their embryonic phenotype and did not form junctions with mature heart cells by 4 weeks... Although neonatal donor cells could form junctions with host myocardium, there was massive initial death of donor cells and at later times the grafts were often isolated by scar tissue... This problem is a direct result of the inflammation and scarring after infarction, and it may be that use of cardiomyocyte transplantation therapy could be more effectively developed to address functional improvement in myopathic heart diseases" (page 602, col. 2, first paragraph). Grounds et al. further teach that although it has been shown in tissue culture that human ES cells can also differentiate into cardiomyocytes, human ES cells have a very low efficiency of conversion into cardiomyocytes compared with those of mice (<10% compared with >80% of murine ES cells; a median of 11 days for differentiation compared with 2 days for murine cells), and that the use of embryonic stem cells as a source of cardiomyocytes is an attractive therapeutic possibility that needs to be fully explored (page 604, col. 2 under the section titled "Embryonic stem cells").

(3) The amount of direction or guidance provided. Apart from the general disclosure that human ES cells can be differentiated into tolerizing cells including mesenchymal stem cells, and that it is possible to differentiate hPS cells into a highly enriched population comprising cardiomyocytes or cardiomyocyte precursors, the instant specification fails to provide any specific guidance including the relevant *in vitro* and *in vivo* examples, for a skilled artisan on how to obtain any effective amount of

mesenchemal stem cells derived from hPS cells with the desired property (e.g., rendering the treated individual immunotolerant to the second cell population) and any effective amount of cardiomyocytes differentiated from hPS cells, and their utilization to attain any therapeutic effects contemplated by Applicants (e.g., repair and/or regeneration and/or reconstituting cardiac function in a treated individual or patient). It is unclear under which specific conditions and/or parameters, an effective amount of tolerizing mesenchymal stem cells or tolerizing cells expressing CD90 or cardiomyocytses could be obtained via the differentiation of hPS cells in culture that can be used for obtaining the contemplated therapeutic effects. Particularly, human ES cells are known to be very inefficient to differentiate into cardiomyocytes even in 2002 (Grounds et al.; Cited above). There is no evidence of record indicating that any of the cell populations differentiated from hPS cells could be survived in an allogenic host environment in a sufficient time period to yield the contemplated therapeutic effects. Fandrich et al. note that the potential for mouse or human embryonic stem cells or their progenitor cells to survive in an allogenic host environment has not been reported, even in 2002, let alone at the effective filing date of the present application (page 176, col. 2, second full paragraph). Moreover, in a related study Bachar-Lustig et al. (Blood 94:3212-3221, 1999; IDS) note that it might be difficult to harvest sufficient Sca-1+Lin- bone marrow progenitor cells in humans at megadoses required for overcoming major transplantation barriers (see abstract). The instant specification also fails to provide any guidance demonstrating that any route of administration of the cardiomyocytes at any site in the treated individual or patient would result in the homing the delivered

differentiated second cell population in an effective amount to the heart to yield the desired therapeutic effects contemplated by Applicants. It is also unclear whether the administered cardiomyocytes are capable of establishing the architecture needed to restore or reconstitute cardiac function in the treated individual and/or how long can they survive.

Since the prior art at the effective filing date of the present application does not provide guidance for the issues discussed above, it is incumbent upon the present application to do so. Furthermore, the physiological art is recognized as unpredictable (MPEP 2164.03).

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues discussed above, the unpredictability of the physiological art particularly the art on tolerance induction and/or cardiac repair or regeneration for human allograft patients using cell populations differentiated from human pluripotent stem cells, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to **make and use** the presently claimed invention.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 12/18/03 (pages 3-8) have been fully considered, but they are not found persuasive.

1. Applicants argue that the specification describes in considerable detail the preparation and growth of pluripotent stem cells (pages 7-10), the making of therapeutic cell populations such as cardiomyocytes (pages 10-12), the making of tolerizing cell

populations such as mesenchymal cells (pages 12-15), and the use of the cell populations to induce tolerance and effect tissue regeneration (pages 15-19).

Examiner notes that the general disclosure that human ES or hPS cells can be differentiated into tolerizing cells including mesenchymal stem cells, and that it is possible to differentiate hPS cells into a highly enriched population comprising cardiomyocytes or cardiomyocyte precursors, and that the use of these cell populations to induce tolerance and effect tissue generation is not deemed to be sufficient guidance for a skilled artisan at the effective filing date of the present application (11/22/2000) to make and use the presently claimed invention in light of the analysis of the Wands factors set forth in the above rejection. There is no evidence of record indicating that at the effective filing date of the present application any effective amount of mesenchemal stem cells or CD90 expressing first cell population derived from hPS cells with the desired property (e.g., rendering the treated individual immunotolerant to the second cell population) and any effective amount of cardiomyocytes differentiated from hPS cells have been successfully generated, and any therapeutic effects contemplated by Applicants (e.g., repair and/or regeneration and/or reconstituting cardiac function in a treated individual or patient) has been achieved through the use of these cell populations *in vivo*.

2. With respect to the references of Waldmann et al., and Sussman cited by Examiner, applicants argue that the Office has the burden of showing that the invention is not adequately enabled by the application, and it is insufficient just to show that the claimed invention has not been done before.

Examiner notes that the references of Waldmann et al. and Sussman are cited to indicate the state of the prior art on tolerance induction and/or cardiac repair or regeneration for human allografts patients at about the effective filing date of the present application. The above enablement rejection is not based exclusively on the references of Waldmann et al. and Sussman, but rather on the overall analysis of the Wands factors.

3. With respect to the reference of Fandrich et al. cited by Examiner on the proposition that embryonic stem cells are not known to survive in an allogeneic host environment, Applicants argue that this is one of the problems that the present invention is designed to solve.

Examiner notes that there is no factual evidence of record indicating that any human embryonic stem cells or their progenitor cells can survive in any allogenic host environment to yield the desired therapeutic effects contemplated by Applicants. Even in the year 2002, about 2 years after the effective filing date of the present application Fandrich et al. still note that the potential for mouse or human embryonic stem cells or their progenitor cells to survive in an allogeneic host environment has not been reported.

4. With respect to the reference of Grounds et al. cited by Examiner on the issue that human ES cells have a very low efficiency of conversion into cardiomyocytes, Applicants argue that the specification provides the same method as that described in US Patent Application 10/193,884 or Xu et al. (Cir. Res. 91:501, 2002) to enrich considerably the proportion of hES derived cardiomyocytes in the preparation.

Examiner notes that the instant specification **has no literal support for the detailed conditions** of the method described in either US Patent Application 10/193,884 (having a later effective filing date) or in the post-filing art of Xu et al. Xu et al. state "The difference in the efficiency of cardiomyocytes differentiation may reflect differences in culture conditions of the undifferentiated hES cells, methods used for the dissociation of hES cells to generate Ebs, the length of EB suspension culture, and/or the quality of serum used for differentiation", and that these differences attribute to a higher percentage of beating Ebs (70% vs 8%) observed by Xu et al. compared with earlier report (page 506, col. 2, first full paragraph). Moreover, even in 2002 Xu et al. still state "[w]e have demonstrated that an enriched population of cardiomyocytes can be derived from hES cells. These hES cell-derived cardiomyocytes can now be tested for ability to enhance cardiac function in preclinical animal models and for utility in drug discovery" (page 507, col. 1, third paragraph), indicating that it was neither routine nor predictable to obtain an effective amount of cardiomyocytes derived from hES cells to attain therapeutic effects contemplated by Applicants at the effective filing date of the present application (11/22/2000). With the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and use the presently claimed invention.

5. With respect to the reference of Bachar-Lustig et al cited by Examiner on the issue that that it is difficult to harvest sufficient Sca-1+ Lin-bone marrow progenitor cells in human at megadoses required for overcoming major transplantation barriers, Applicants argue that embryonic stem cells can be grown up to any volume desired, and

using hES cells as a source of the toleragenic cell population rather than human bone marrow can provide any volume of cells that is required.

Examiner notes that there is no evidence of record indicating that at the effective filing date of the present application any effective amount of mesenchemal stem cells or CD90 expressing first cell population derived from hPS cells with the desired property (e.g., rendering the treated individual immunotolerant to the second cell population) has been attained.

6. With respect to the use of cells for cardiac repair, Applicants argue that there are a number of trials under way at the preclinical and clinical stage showing considerable efficacy as evidenced by the reported results of a Phase I trial in which human patients were treated with autologous skeletal myoblast transplantation by Menasche et al. (J. Am. Coll. Cardiol. 41:1078, 2003), and the reported results of an animal model in which isogenic fetal cardiomyocytes grafted into the ischemic heart, and were still present after 10 months by Yao et al. (J. Mol. Cell. Cardiol. 35:661, 2003). Therefore, the viability of using cardiomyocytes in therapy being well established.

Examiner notes that the reported results in the post-filing arts of Menasche et al. and Yao et al. are irrelevant to the presently claimed invention. This is because neither post-filing arts utilize the same method steps and starting materials (e.g., administering toleragenic and cardiomyocyte cell populations derived from hPS cells) to attain the therapeutic effects contemplated by Applicants.

7. With respect to the issue of the ability of hES-derived cells to induce tolerance, Applicants submitted data in Appendix B (the same data is discussed in the Declaration under 37 CFR 1.132 filed 12/24/03) demonstrating that hES cells or neural progenitors obtained from hES cells have the ability to suppress reactivity of allogeneic cells in a mixed lymphocyte reaction (MLR), and Applicants argue that hES-derived toleragenic cells appear to have the same properties in mixed lymphocyte reactions conducted in culture as toleragenic cells obtained from bone marrow such as mesenchymal stem cells and hematopoietic cells of various kinds. Applicants further cited published patents and articles confirming that mesenchymal cells and hematopoietic cells can be used to enhance survival of tissue allografts as evidenced by the teachings of Seung et al. (J. Clin. Invest. 112:795, 2003), U.S. Patent No. 6,368,636), Kuhr et al. (Transplantation 73:1487, 2002), Barber et al. (Transplantation 51:70, 1991, Abstract), Fontes et al. (Lancet 3434:151, 1994, Abstract) and Rifle et al. (Transplantation 75 Suppl:3S, 2003). Thus, all the elements of the claimed invention should work in the same manner as indicated.

It is noted that hES cells or neural progenitors obtained from hES cells **are not the same** as mesenchymal stem cell populations or CD90 expressing cell populations derived from hPS cells that have the desired immunotolerant property (e.g., rendering the treated individual immunotolerant to a second cell population) to be utilized in the presently elected invention. Additionally, the results obtained from an *in vitro* MLR assay are not reasonable correlated to any *in vivo* therapeutic effects contemplated by Applicants in light of the analysis of the Wands factors already discussed above.

Moreover, Kuhr et al. (Transplantation 73:1487, 2002; Cited by Applicants) state "*In vitro* assays of alloimmune response, such as mixed lymphocyte reaction (MLR), **have not proven reliable for determining responsiveness between DLA-identical canines differing only in minor MHC antigens**. Therefore, we have relied on the results from the kidney allografts and the prompt, severe rejection found in all donor animals are sufficient for an alloimmune response" (page 1491, col. 2, last line continues to first paragraph of col. 1 on page 1492). Furthermore, Applicants even state that hES-derived toleragenic cells **appear to have the same properties** in mixed lymphocyte reactions conducted in culture as toleragenic cells obtained from bone marrow such as mesenchymal stem cells and hematopoietic cells of various kinds. This is not a factual evidence indicating that hES-derived mesenchymal stem cell population or CD90-expressing first cell population would have tolerant property to yield the desired therapeutic effects contemplated by Applicants.

None of the teachings in the references of Seung et al., U.S. Patent No. 6,368,636, Kuhr et al., Barber et al., Fontes et al. and Rifle et al. that are cited by Applicants involves with any toleragenic cell population and/or cardiomyocytes derived from hES or hPS cells. Since the method steps and the starting materials are not the same as those of the present elected invention, their reported results are irrelevant to the instant claims particularly for the post-filing arts of Seung et al., U.S. Patent No. 6,368,636; Kuhr et al. and Rifle et al.

The Declaration under 37 CFR 1.132 filed 12/24/03 is insufficient to overcome the rejection of claims 1-20 based upon insufficient guidance provided by the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to **make and/or** use the invention under 35 U.S.C. 112, first paragraph. This is because as already noted above, hES cells or neural progenitors obtained from hES cells **are not the same** as mesenchymal stem cell populations or CD90 expressing cell populations derived from hPS cells that have the desired immunotolerant property (e.g., rendering the treated individual immunotolerant to a second cell population) to be utilized in the presently elected invention. Additionally, the results obtained from an *in vitro* MLR assay are not reasonable correlated to any *in vivo* therapeutic effects contemplated by Applicants in light of the analysis of the Wands factors already discussed above. Moreover, Kuhr et al. (Transplantation 73:1487, 2002; Cited by Applicants) state "*In vitro* assays of alloimmune response, such as mixed lymphocyte reaction (MLR), **have not proven reliable for determining responsiveness between DLA-identical canines differing only in minor MHC antigens**. Therefore, we have relied on the results from the kidney allografts and the prompt, severe rejection found in all donor animals are sufficient for an alloimmune response" (page 1491, col. 2, last line continues to first paragraph of col. 1 on page 1492).

Accordingly, claims 1-20 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for the reasons already set forth above.

Conclusions

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (703) 872-9306.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER